



A STUDY OF DRY EYE DISEASE AT IIUM
OPTOMETRY CLINIC

BY

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ABSTRACT

Dry eye (DE) is a multifactorial pathology which affects tear production and evaporation rate; and associated with diabetes mellitus (DM). The prevalence of DE is 7 to 34% worldwide. In Malaysia, however, the prevalence data and studies on the associations between DE symptoms and signs are limited. In addition, there is no data on tear functions assessments of diabetic patients. Therefore, the aims of this study were to determine the prevalence of dry eye disease (DED); identify the associations between DE symptoms and signs; and compare DE symptoms and signs between DM and non-DM; DM with and without DED in the Optometry Clinic International of the Islamic University Malaysia (IIUM) Kuantan. A retrospective analysis of DE and tear break up time test (TBUT) values were assessed in 643 files. Based on the diagnosis of dry eye from at least one reported symptom or TBUT < 5 seconds, the overall prevalence of DED was 48.8%, which was mainly due to the high number of diabetics and contact lens (CL) wear. Fifteen percent of the DE was based on symptoms while 26.7% by TBUT, indicating the importance of clinical sign in DE diagnosis. The prevalence of DED was higher in females than males. This might be due to the difference in the acinar size of lacrimal glands between the two genders, responsible for a higher tear volume in males than females. The prevalence of DED increased with age, 44.9% in < 50 years and 56.1% in \geq 50 years (males); and 43.0% in \leq 49 years and 68.4% in > 50 years (females) because of the alteration in tear function with increasing age. The risk factors associated with symptomatic dry eye disease were CL wear (adjusted OR=3.4; 95% CI=1.2-9.3) and a lower TBUT values (adjusted OR=2.3; 95% CI=1.0-5.1) in males. The study found that age \geq 50 years (adjusted OR=1.9; 95% CI=1.0-3.6) and a lower tear meniscus height (adjusted OR=3.8; 95% CI=2.3-6.3) scores were the risk factors for dry eye symptoms in females. DM with DED had a significantly higher frequency of dry eye symptoms than DM without DED ($p < 0.001$). TBUT was significantly different between DM and non-DM; DE ($p < 0.001$) and between the DM (DE and the non-DE) ($p < 0.05$). In addition, the number of patients with dry eye symptoms was significantly higher in diabetics than non-diabetics. Similarly, the number of diabetics with dry eye symptoms was significantly higher than diabetics without dry eye symptom ($p < 0.001$). This study provided new information about the prevalence of dry eye disease and its risk factors in the East Coast of Peninsular Malaysia. Also, the results of this investigation may enhance the understanding of the relationship between DM and tear functions. In conclusion, the prevalence of DED among optometric outpatients is comparatively high with almost 50% of them diagnosed with dry eye disease. Symptoms and signs were poorly associated. Additionally, DED is more common among DM patients.

خلاصة البحث

جفاف العين هو مرض متعدد الأسباب يؤثر على إنتاجية الدموع وتبخرها ومصاحب لمرض السكري. معدل انتشار جفاف العين في جميع أنحاء العالم هو ٧ إلى ٣٤ بالمئة. مع ذلك فإن البيانات والدراسات حول انتشار جفاف العين و العلاقة مابين أعراض وعلامات المرض محدوده في ماليزيا. و بالإضافة الى ذلك، لاتوجد بيانات عن عمليات تقييم وظائف المسيل للدموع لمرضى السكري. لذلك، كانت أهداف هذه الدراسة هو تحديد مدى انتشار جفاف العين؛ تحقق العلاقة مابين أعراض وعلامات المرض. ومقارنة أعراض وعلامات جفاف العين بين مرضى السكري والأشخاص الطبيعيين؛ أيضا مرضى السكري الذين يعانون من جفاف العين و الذين لا يعانون من أعراض وعلامات جفاف العين في عيادة البصريات الجامعة الإسلامية العالمية-كوانتان ماليزيا. تم تقييم وتحليل أعراض وعلامات المرض باثر رجعي لحوالي ٦٤٣ ملف. تم تشخيص جفاف العين بناء على أعراض وعلامات المرض من خلال المريض أو الفاحص. كان معدل جفاف العين في هذه الدراسة حوالي ٤٨ بالمئة، وهو مايعزى أساسا إلى ارتفاع عدد مرضى السكري ومرتدي العدسات اللاصقة. واستند خمسة عشر في المئة من مرضى جفاف العين إلى أعراض المرض في حين أن ٢٦ بالمئة إلى علامات المرض. مما يدل على أهمية فحص الأخصائي في تشخيص المرض. وكان انتشار معدل جفاف العين في هذه الدراسة في الإناث أكثر من الذكور. قد يكون هذا يرجع إلى اختلاف في حجم عنينية من الغدد الدمعية بين الجنسين، مسؤولة عن حجم أعلى المسيل للدموع في الذكور أكثر من الإناث. ازداد معدل جفاف العين مع التقدم في السن، ٤٤ بالمئة في الذكور الذين أعمارهم تقل عن خمسين سنة بينما ٥٦ بالمئة في الذكور الذين أعمارهم تزيد عن خمسين سنة؛ ٤٣ بالمئة في الإناث الذين أعمارهم تقل أو تعادل تسعة وأربعين سنة بينما ٦٨ بالمئة في الإناث الذين أعمارهم تزيد عن خمسين سنة بسبب تغيير في وظيفة المسيل للدموع مع زيادة العمر. وكانت عوامل الخطر المرتبطة بأعراض جفاف العين في الذكور هي ارتداء العدسات اللاصقة و معدلات إنخفاض (TBUT). ووجدت الدراسة أن الأناث فوق سن الخمسين سنة و معدلات إنخفاض (TMH) هي من عوامل الخطر المرتبطة بأعراض جفاف العين. مرضى السكري الذين يعانون من جفاف العين يمتلكون نسبة عالية من أعراض جفاف العين مقارنة بمرضى السكري الذين لا يعانون من أعراض المرض ($p < 0.001$). معدلات إنخفاض (TBUT) تتناسب تناسباً طردياً مع مرضى السكري وأيضا مع مرضى السكري الذين يعانون من جفاف العين ($p < 0.05$). و بالإضافة الى ذلك، عدد المرضى الذين يعانون من علامات وأعراض جفاف العين تتناسب طردياً مع مرضى السكري. ($p < 0.001$). هذه الدراسة زودت معلومات جديدة عن مدى انتشار وعوامل الخطر لمرض جفاف العين في الساحل الشرقي لماليزيا. أيضا، فإن نتائج هذا التحقيق قد تعزز فهم العلاقة بين مرضى السكري وتأثر المسيل للدموع. وفي الختام، معدل المصابين بجفاف العين في مختبر البصريات الطبية يقارب ٥. بالمئة. العلاقة ضعيفة بين أعراض وعلامات جفاف العين. و بالإضافة الى ذلك، مرض جفاف العين أكثر شيوعاً في مرضى السكري.

APPROVAL PAGE

I certify that I have supervised and read this study and that in my opinion, it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a thesis for the degree of Master of Health Sciences (Optometry).

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DECLARATION

I hereby declare that this dissertation is the result of my own investigations, except where otherwise stated. I also declare that it has not been previously or concurrently submitted as a whole for any other degrees at IIUM or other institutions.

Mohammed A.M Aljarousha

Signature

Date

INTERNATIONAL ISLAMIC UNIVERSITY MALAYSIA

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In the name of Allah, Most Gracious, Most Merciful
Peace Be Upon Him Our Prophet, Muhammad S.A.W.

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This thesis is dedicated to Martyrs of Palestine

TABLE OF CONTENTS

Abstract	i
Abstract in Arabic	ii
Approval Page	iii
Declaration	iiiv
Copyright Page.....	v
Acknowledgements	vi
Table of contents	vii
List of Tables	xi
List of Figures	xii
List of Abbreviations	xvi
List of Symbols	xvii
CHAPTER ONE: INTRODUCTION	1
1.1 Background and justification of study	1
CHAPTER TWO: LITERATURE REVIEW	7
2.1 Dry Eye Disease Diagnosis	7
2.1.1 Prevalence and Incidence of Dry Eye Disease in Malaysia.....	7
2.1.2 Epidemiological Data from Dry Eye Studies.....	9
2.2 Risk Factors in the Prevalence of Dry Eye Disease	11
2.2.1 Age versus Dry Eye	12
2.2.2 Gender and Dry Eye.....	13
2.2.3 Medications	14
2.2.4 Contact Lens Wear.....	15
2.2.5 Ophthalmic Surgery	15
2.2.6 Anterior Segment Diseases and Physiological Changes.....	16
2.2.7 Systemic Diseases	17
2.2.8 Tear Volume	20
2.2.9 Environmental Stimuli and Computer Use	20
2.2.10 Dry Eye in Urban versus Rural Areas.....	21
2.3 Tears	21
2.3.1 Tear Structure.....	21
2.3.2 Tear Composition and Biochemistry	23
2.3.3 Tear Dynamics and Distribution	23
2.3.4 Tear Evaporation and Drainage	25
2.4 Dry Eye Syndrome	26
2.4.1 Classification of the Major Causes of Dry Eye.....	26
2.4.1.1 Aqueous Tear-Deficient Dry Eye	26
2.4.1.2 Evaporative Dry Eye	30
2.5 Diagnose of Dry Eye	33
2.5.1 Screening for Dry Eye.....	34
2.5.2 Clinical Diagnose of Dry Eye	39
2.5.2.1 Tear Break up Time Test	39
2.5.2.2 Schirmer Tear Test	40
2.5.2.3 Phenol Red Thread Test	41

2.5.2.4 Rose Bengal Staining.....	42
2.5.2.5 Lissamine Green Staining.....	42
2.5.2.6 Fluorescein Staining	43
2.5.2.7 Tear Meniscus Height.....	43
2.5.2.8 Tear Film Osmolarity	44
2.6 Summary	45
2.7 Research Objectives	46
2.8 Research Questions	46
CHAPTER THREE: MATERIALS AND METHODS	47
3.1 Introduction.....	47
3.2 Study Design.....	47
3.3 Data Extraction	48
3.3.1 Past Ocular History	49
3.3.2 Systemic Diseases and Medications	51
3.3.3 Symptoms of Dry Eye Disease	51
3.3.4 Clinical Sign of Dry Eye.....	52
3.3.4.1 Tear Break up Time Test.....	52
3.3.5 Tear Film Evaluation	56
3.3.5.1 Tear Meniscus Height.....	56
3.3.6 Ocular Surface Integrity.....	56
3.3.6.1 Corneal Fluorescein Staining.....	56
3.4 Subjects.....	58
3.4.1 Inclusion Criteria.....	58
3.4.2 Exclusion Criteria	58
3.5 Statistical Analysis.....	58
3.6 Conclusion	59
CHAPTER FOUR: RESULTS	61
4.1 Introduction.....	61
4.2 Dry Eye Disease Prevalence.....	61
4.2.1 Prevalence of Dry Eye Disease by Gender	62
4.2.1.1 Prevalence of Clinically Diagnosed DED based on TBUT or \geq One DED Symptom	62
4.2.1.2 Prevalence of Clinically Diagnosed DED based on TBUT	62
4.2.1.3 Prevalence of \geq One Symptom of DED	62
4.2.2 Prevalence of Dry Eye Disease by Age	65
4.2.2.1 Prevalence of Clinically Diagnosed DED based on TBUT or \geq One DED Symptom between Ages (< 50 vs. \geq 50-Years Old Females)	65
4.2.2.2 Prevalence of Clinically Diagnosed DED based on TBUT or \geq One DED Symptom between Ages (< 50 vs. \geq 50-Years Old Males)	65
4.2.2.3 Prevalence of Clinically Diagnosed DED based on TBUT between Ages (< 50 vs. \geq 50-Years Old Females)	65
4.2.2.4 Prevalence of Clinically Diagnosed DED based on TBUT between Ages	

(< 50 vs. \geq 50-Years Old Males)	66
4.2.2.5 Prevalence of \geq One DED Symptom between Ages (< 50 vs. \geq 50-Years Old Females)	66
4.2.2.6 Prevalence of \geq One DED Symptom between Ages (< 50 vs. \geq 50-Years Old Males)	66
4.3 Univariate Analysis	68
4.3.1 Males	68
4.3.2 Females	71
4.4 Multivariate Logistic Regression Model to Identify Predictors of the Dry Eye Symptoms	74
4.4.1 Males	74
4.4.2 Females	75
4.5 Comparison of Dry Eye Symptoms and Clinical Signs Scores between Diabetic and Non-diabetic Subjects	76
4.5.1 Frequency of Dry Eye Symptoms between Diabetic and Non- diabetic Subjects	77
4.5.2 Comparison of Clinical Signs Scores between Diabetic and Non-diabetic Subjects	78
4.5.2.1 Comparison of Tear Break up Time Test Values between Diabetic and Non-diabetic Subjects	78
4.5.2.2 Comparison of Tear Meniscus Height Values between Diabetic and Non-diabetic Subjects	78
4.5.2.3 Comparison of Corneal Staining grades between Diabetic and Non-diabetic Subjects	79
4.6 Comparison of Tear Functions between Diabetic Subjects with and without Dry Eye Disease.....	80
4.6.1 Frequency of Dry Eye Symptoms between Diabetic Subjects with and without Dry Eye Disease	80
4.6.2 Comparison of Clinical Signs Scores between Diabetic and Non-diabetic Subjects.....	81
4.6.2.1 Comparison of Tear Break up Time Test Values between Diabetic Subjects with and without Dry Eye Disease.....	81
4.6.2.2 Comparison of Tear Meniscus Height Values between Diabetic Subjects with and without Dry Eye Disease.....	81
4.6.2.3 Comparison of Corneal Staining grades between Diabetic Subjects with and without Dry Eye Disease	81
CHAPTER FIVE: DISCUSSION.....	83
5.1 Dry Eye Disease Prevalence	83
5.2 Factors Affecting the Prevalence of Dry Eye	89
5.2.1 Diabetics.....	89
5.2.1.1 Diabetics vs non-Diabetics	89
5.2.1.2 Diabetics with Dry Eye vs Diabetics without Dry Eye	91
5.2.2 Contact Lens Wear.....	92
5.2.3 Gender and Age	94
5.2.4 Other Contributing Factors	96

5.3 Association between Dry Eye Symptoms and Clinical Tests.....	97
5.3.1 Tear Break up Time Test	97
5.3.2 Corneal Staining.....	99
5.3.3 Tear Meniscus Height	100
5.4 Conclusion	100
CHAPTER SIX: CONCLUSION	103
6.1 Conclusion	103
6.2 Limitation of the Study	105
6.3 Recommendation for Future Research	106
REFERENCES.....	110
APPENDIX A: Patient’s Consent Form	136
APPENDIX B: Pre-submission Screening Document.....	138
APPENDIX C: Related Publication	141
APPENDIX D: Abstract for Exhibition and Congress	142

LIST OF TABLES

<u>Table No.</u>		<u>Page No.</u>
2.1	Summary of other Studies on the Prevalence (%) of Dry Eye Disease	11
2.2	Major Risk Factors for the Dry Eye Syndrome	12
2.3	Comparison with Previous Reported Sex-Specific Percentage of Dry Eye	14
2.4	Ocular Risk Factors for Meibomian Gland Dysfunction	33
2.5	Common Symptoms Reported by Patients with Ocular Surface Disease	35
3.1	Diagnostic cut-off Scores for Clinical Dry Eye Disease in the Present Study	52
4.1	Prevalence (%) of Signs and any Symptoms of Dry Eye by Gender	64
4.2	Prevalence (%) of Signs and any Symptoms of Dry Eye by Age	67
4.3	Spermmans' Correlation between Dry Eye Symptoms and Panel of Variables in Males	68
4.4	Spermmans' Correlation between Dry Eye Symptoms and Panel of Variables in Females	71
4.5	Multivariate Logistic Regression Model to Identify Predictors of the Dry Eye Symptoms in Males	75
4.6	Multivariate Logistic Regression Model to Identify Predictors of the Dry Eye Symptoms in Females	76
4.7	Subjects Characterstics	77
4.8	Frequency of Dry Eye Symptoms between Diabetic and non-Diabetic Subjects	78
4.9	Comparision of Clinical Signs Scores between Diabetic and non-Diabetic Subjects	79
4.10	Comparision of Clinical Signs Scores between Diabetic Subjects with and without Dry Eye	80
5.1	Summary of Other Studies on the Prevalence (%) of Dry Eye based on Different Definitions	84

LIST OF FIGURES

<u>Figure No.</u>		<u>Page No.</u>
1.1	The Lacrimal Functional Unit (LFU)	4
2.1	Three Layers Structures of The Tear Film	23
2.2	A schematic Diagram of the Tear Pathway	24
2.3	Etiopathogenesis of Dry Eye Disease	27
2.4	Classification and Major Aetiology Causes of Aqueous-Deficient Dry Eye	29
2.5	Meibomian Sebaceous Gland	31
3.1	Flow Chart of the Present Study	48
3.2	Medical Files Collected Involved (Date of the first Examination, Age at First Visit, Major Symptoms, Ocular History, General Health, Medications, and Best Visual Acuity)	50
3.3	Slit Lamp Biomicroscope (SL-102/203)	53
3.4	Fluorescein Tear Break up Time Test	54
3.5	Details of Tear Film and Ocular Surface Integrity Evaluation Include (Tear Break up Time Test, Tear Meniscus Height, Corneal Staining)	55
3.6	Slit Lamp View of the Tear Meniscus	56
3.7	Efron Grading of the Corneal Fluorescein Staining	67
4.1	Percentages of Dry Eye based on Symptoms, Signs, both and non-Dry Eye	62
4.2	No Significant Association between Dry Eye Symptoms and Age in Male Subjects (n=244)	69
4.3	Significant Association between Dry Eye Symptoms and Tear Break up Time Test in Male Subjects (n=244)	69
4.4	No Significant Association between Dry Eye Symptoms and Corneal Staining in Male Subjects (n=244)	70
4.5	No Significant Association between Dry Eye Symptoms and Tear Meniscus Height in Male Subjects (n=244)	70

4.6	No Significant Association between Dry Eye Symptoms and Age in Female Subjects (n=399)	72
4.7	No Significant Association between Dry Eye Symptoms and Tear Break up Time Test in Female Subjects (n=399)	72
4.8	No Significant Association between Dry Eye Symptoms and Corneal Staining in Female Subjects (n=399)	73
4.9	Significant Association between Dry Eye Symptoms and Tear Meniscus Height in Female Subjects (n=399)	73
4.10	Frequency of Dry Eye Symptoms between Diabetic Subjects with and without Dry Eye	82
6.1	Algorithm for Screening of Diabetes Mellitus to Determine Dry Eye Patients	108

LIST OF ABBREVIATIONS

DED	Dry Eye Disease
DM	Diabetes Mellitus
LFU	Lacrimal Functional Unit
USD	United States Dollars
RGP	Rigid Gas Permeable
PRT	Phenol Red Thread
TBUT	Tear Break up Time Test
CFS	Corneal Fluorescein Staining
STT	Schirmer Tear Test
IIUM	International Islamic University Malaysia
UMMC	University Malaya Medical Center
US	United States
MGD	Meibomian Gland Dysfunction
LASIK	Laser-Assisted in situ Keratomileusis
TED	Thyroid Eye Disease
HRT	Hormone Replacement Therapy
DR	Diabetic Retinopathy
RH	Relative Humidity
VDT	Visual Display Terminal
VIP	Vasoactive Intestinal Peptide
ADDE	Aqueous-Deficient Dry Eye
SSDE	Sjögren's Syndrome Dry Eye
EDE	Evaporative Dry Eye
DEQ	Dry Eye Questionnaire
OSDI	Ocular Surface Disease Index
CLDEQ	Contact Lens Dry Eye Questionnaire
OCI	Ocular Comfort Index
WHS	Women's Health Study
MCDEQ	McMonnies Dry Eye Questionnaire
NIBUT	Non-Invasive Break up Time
CTT	Cotton Thread Test
BCVA	Best Corrected Visual Acuity
LE	Left Eye
OR	Odds Ratio
CI _s	Confidence Interval
SD	Standard Deviation
IQR	Interquartile range
SEE	Salisbury Eye Evaluation
IDDM	Insulin Dependent Diabetes Mellitus
NIDDM	Non-insulin Dependent Diabetes Mellitus
n	Number of Participants
sec	Second
mm	Millimeter

LIST OF SYMBOLS

%	Percent
>	More than
<	Less than
\geq	Greater than or equal to
\pm	Plus-Minus
=	Equal to
p	Probability
-	To
r	Spearman's Correlation Coefficient
*	Statistical significance denotation

CHAPTER ONE

INTRODUCTION

1.1 BACKGROUND AND JUSTIFICATION OF STUDY

Dry eye disease (DED) is a multifactorial pathology that can affect ocular comfort, vision, and tear film stability, and can damage the ocular surface [Dry Eye Workshop report (DEWS)] (Lemp et al., 2007). The disease is also commonly known as a keratoconjunctivitis sicca or dysfunctional tear syndrome which is a distressing condition for both patients and eye care providers (Behrens et al., 2006). According to Lemp et al. (2007) and Bron et al. (2009), DED is a specific ocular condition caused by various aetiologies. However, most DED cases are characterised by tears instability and hyperosmolarity (Li et al., 2004; Lemp et al., 2011). DED is among the most frequently reported eye problems, with an estimated prevalence of 7% to 34% across the globe. For instance, the prevalence of dry eye disease in Indonesia is 27.5%, Spain 11%, China 23.7%, India 16.4%, Singapore 12.3%, and Turkey 8.3% (Lee et al., 2002; Viso et al., 2009; Zhang et al., 2012; Rege, 2013; Tan et al., 2015; Yilmaz et al., 2015). Rates vary widely because of different diagnostic criteria used in reported studies.

A higher incidence of the disease has been reported among the elderly population (≥ 50 years of age) compared to younger age groups (McCarty et al., 1998; Lin et al., 2003; Moss et al., 2008). Most studies also found that the prevalence of DED is about twice as high in female compared to male (Moss et al., 2000; Sahai and Malik, 2005; Gupta et al., 2010). Furthermore, populations of the Asian and Hispanic inheritance are at higher risk of developing DED compared to other race group,

suggesting possible genetic factors (Lin et al., 2003; Schumberg et al., 2003; Uchino et al., 2006).

Dry eye disease is characterised by a progressive dysfunction of the lacrimal and meibomian glands that typically leads to decreased aqueous tear production and increased tear evaporation, respectively. It is often accompanied by insufficient tears to lubricate and nourish the eye (Lemp et al., 2007). People with keratitis sicca either do not generate sufficient tears or experience a malfunction of the tear film. In addition, the dry eye may occur due to inadequate aqueous tear production and exacerbated tear evaporation (Lemp et al., 2007). Specifically, Bron et al. (2014) reported that the patient with meibomian gland dysfunction is at a high risk of developing a severe dry eye.

Dry eye has been associated with systemic diseases such as diabetes mellitus (DM), hypertension, arthritis, gout, thyroid disease, fractures and osteoporosis (Moss et al., 2000; Moss, 2004; Jie et al., 2009). Diabetes may affect the human body system and organs, which the eye is not spared from. Diabetic retinopathy is the 5th leading cause of blindness globally. DM has become a major public health concern in recent time. The global prevalence of diabetes is estimated to be 246 million in 2007 and would possibly reach up to 380 million by 2025 (International Diabetes Federation, 2006). Approximately, 80% of diabetes cases occur in the developing world, with South East Asian countries having the highest burden of diabetes (Lee et al., 2006). Malaysia is reported to have a prevalence of 9.9% and projected to rise up to 12.3% by 2025, thus making it one of the worst affected countries in Asia (King et al., 1998; International Diabetes Federation, 2006). Diabetic subjects demonstrated dry eye symptoms that were also supported by the affected scores of the clinical tests. It is critical for clinicians to know about alterations in tear functions in diabetic subjects to

initiate a proper management for dry eye which may affect their quality of lives. Dry eye disease was reported to be significantly higher in diabetic patients aged 50 years and above when compared with non-diabetic subjects (Kaiserman et al., 2005). A higher prevalence of dry eye symptoms and signs were also found in non-insulin dependent diabetes mellitus (NIDDM) patients (Idu and Oghre, 2010). The same group of researchers postulated that parasympathetic innervation alteration in NIDDM patients could lead to the reduced nervous supply in the lacrimal glands and thereby decreases aqueous tear secretion. In addition, reflex tear secretion that is associated with corneal irritation has been found to be highly dependent on the sensitivity of the cornea (Inoue et al., 2001). The reduced corneal sensitivity in the diabetic patients consequently leads to further reduction in the reflex tear secretion (Taylor et al., 1981; Tabatabay et al., 1988; Tsubota et al., 1991; Goebbels, 2000). Goblet cells of the conjunctiva secrete the mucin portion of the tears and contribute to tear film stability (Lemp et al., 1970; Mandell, 1988). Therefore, it has been implied that the diminished tear film stability in diabetic patients is at least partially caused by the goblet cell loss (Dogru et al., 2001).

The lacrimal functional unit (LFU) is composed of the eyelids, meibomian glands, cornea, lacrimal glands, conjunctiva, and the sensory and motor nerves connecting these structures that all assist in stabilising the tear film (Stern et al., 1998) [Figure 1.1]. The overall function of the LFU is to maintain the corneal transparency, the integrity of the tear film and protect the ocular surface (Stern et al., 1998; Stern et al., 2004). However, dry eye is considered to be a disruption or failure of the LFU. This pathology involves disorder or impairment of the lacrimal glands and sensory and motor nerves that compromise the structure of the tear film (layers). Subsequently, this leads to the destabilisation of the tear film through reduced aqueous

tear production, paused tear clearance and altered tear composition (Stern et al., 1998; Stern et al., 2004; Lemp et al., 2007).

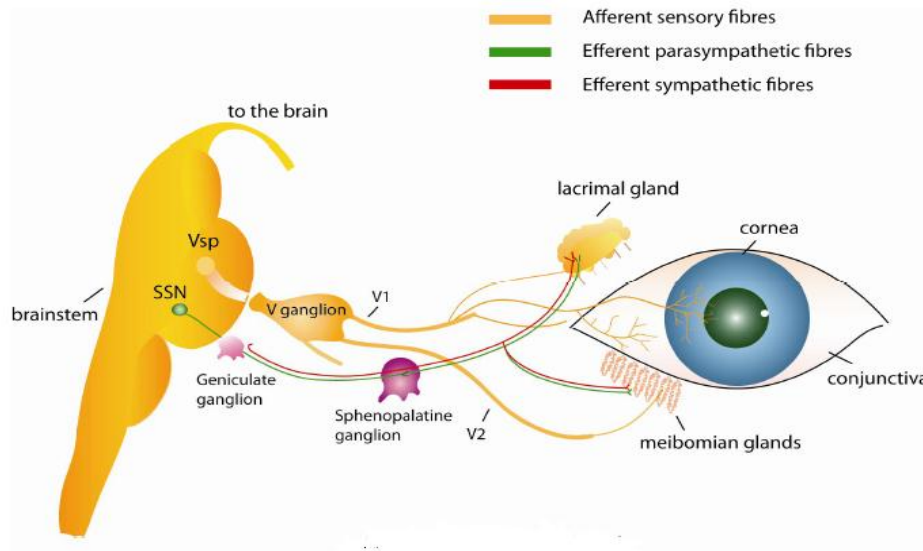


Figure 1:1 The Lacrimal Functional Unit (LFU)
Source: (Situ, 2010)

Dry eye disease may impair functional visual acuity, contrast sensitivity, and vision-related quality of life, which reduces the ability to read, drive, use a computer, and watch television for prolonged periods (Miljanović et al., 2007; Patel et al., 2011). Subjects with moderate or severe dry eye syndrome often become frustrated and experience great discomfort, which limits their lifestyle activities, as well as their occupational productivities (Lin and Yiu, 2014). Dry eye patients are two to three times more likely to experience difficulties to perform day to day activities compared to those without the condition (Miljanovic et al., 2007).

Dry eye symptoms include stinging, grittiness, soreness, eye watering, light sensitivity and deteriorating vision (Begley et al., 2003; Simpson et al., 2008; Labbé et

al., 2013). Even though these symptoms seem mild, they may cause many difficulties and affect the quality of life (Smith, 2007; Tavares, 2010). The presence of dry eye disease on the ocular surface can cause serious irritation to the interpalpebral ocular surface, particularly the cornea. Also, it is commonly found to be chronic, particularly in the middle or older aged patients (Moss et al., 2000; Moss, 2004).

The significant socio-economic implications of dry eye disease include increased health-care costs (Miljanovic et al., 2007; Tong et al., 2010; Pouyeh et al., 2012). The evaluation of the costs implication, however, is problematic because dry eye is a multifactorial disease. For instance, In the United States the cost of managing dry eye was estimated at USD 700,000 per million subjects (Muñoz, 2000). In addition, the annual health-care cost ranged from USD 270,000 in France to USD 1.10 million in the United Kingdom for every 1,000 dry eye syndrome subjects (Clegg et al., 2006).

In Malaysia, the prevalence of dry eye disease data and studies on the associations between dry eye symptoms and signs are limited. At present, only two publications are readily available, the first is a prevalence study of dry eye in University Malaya Medical Center (UMMC) based on a prospective study and the other is an incidence study of dry eye disease in a sample population in Kuala Lumpur. The prevalence study in UMMC was performed in 2002, at a time the definition of dry eye disease was a non-specific condition. In 2007, however, dry eye disease became a specific term (Lemp et al., 2007). Therefore, the incidence study in Kuala Lumpur was carried out after the definition of dry eye disease has become a specific disease. Scientifically, there is a difference between prevalence and incidence. Prevalence is the number or proportion of all new and old patients with a disorder or occurrence of an event during a certain period. On the contrary, incidence is the rate at

which a particular event occurs, as the number of new patients with a specific disorder occurring during a certain period in a population at risk (Shields and Twycross, 2003). Both studies were carried out in Kuala Lumpur, the west coast of Malaysia. The prevalence of dry eye disease varies with location and depends on the type of clinical examination, its method of diagnosis and the population under study (Schaumberg et al., 2003).

The current study is the first to look at the prevalence of dry eye in the East Coast of Peninsular Malaysia with sandy beaches, more winds and prolonged spells of rains (Juneng et al., 2007). The East Coast of Malaysia was chosen because of its low relative humidity, closeness to rural area and lower level of education (Department of Statistics, Malaysia, 2010; Arshad et al., 2012). Additionally, the study is also justified by the fact that only a few studies have evaluated the Asian population (Jamaliah and Fathilah, 2002; Lu et al., 2008; Jie et al., 2009; Tong et al., 2010). To our knowledge, the present study is the first retrospective study of dry eye syndrome in Malaysia. The study also covered an extensive period of 7 years compared to the five years study period by other researchers in the US (Galor et al., 2011; Lemp et al., 2012).

The present study also investigates the associations between dry eye symptoms and signs while identifying predictors of dry eye symptoms from a panel of variables which include age, contact lens wear, tear break up time test, corneal fluorescein staining, and tear meniscus height which has not been performed in Malaysia. Also, this study is a novel experiment on accessing tear film in diabetic patients, especially in Malaysia, which enhance the understanding of the relationship between the diabetes mellitus and tear film.

CHAPTER TWO

LITERATURE REVIEW

2.1 DRY EYE DISEASE DIGNOSIS

A large number of various clinical studies of the dry eye prevalence depend only on reports of symptoms for the definition of the disease (Hikichi et al., 1995; Doughty et al., 1997; Chia et al., 2003). One of the studies recommends that the evaluation of dry eye by symptoms alone is adequate because dry eye seldom progresses to the stage of causing ocular damage without symptoms being present (Schein et al., 1997). However, recent reports suggest that symptoms alone are not sufficient for the diagnosis of a dry eye because the same symptoms can be experienced by subjects with a large range of ocular surface conditions and tear film disorders (Pflugfelder et al., 1998). In addition, symptoms and signs of dry eye are required for examination and assessment of prevalence rates. A report suggested that in the eye care specialist clinic that received a large number of patients with dry eye syndrome, approximately one person in every four patients have complaints related to dry eye (Brewitt and Sistani, 2001). Furthermore, 17% of the total number of the clinical visits to eye clinics is due to dry eye (O'Brien and Collum, 2004).

2.1.1 Prevalence and Incidence of Dry Eye Disease in Malaysia

Malaysia is a multiracial country with three major races, namely: Malays, Chinese, and Indians. Studies on dry eye diseases in Malaysia are very scarce. Therefore, only very few published data are available. In a study by University Malaya Medical Center (UMMC), the prevalence of Chinese patients with a decrease or unstable tear

film leading to the diagnosis of dry eye was 40.2% compared with 35.6% for Malays and 24.6% for Indians (Jamaliah and Fathilah, 2002). The dry eye disease in UMMC was defined as the presence of symptoms and abnormal test results such as Phenol red thread (PRT) test, Schirmer tear test (STT), tear break up time test (TBUT) and corneal fluorescein staining (CFS). From 200 patients, the presence of dry eye from the abnormal test results showed that 78 (39%) of 200 patients had TBUT less than 8 seconds, 26 patients (13%) had Schirmer test of less than 5 mm and 9 patients (4.5%) had PRT less than 10 mm, 50 patients (25%) had diminished or scanty marginal tear film, 8 patients (4%) had corneal staining more than 1/3 of the cornea.

Another study, which investigated the percentage of dry eye disease in Kuala Lumpur, was conducted by Mohd-Ali et al. (2011). Their sample consisted of 900 adult participants, which was examined at 2 to 3 months for data collection. The incidence of dry eye disease in the study was estimated using the McMonnies dry eye questionnaire. Approximately 15% of the sample population had symptoms of dry eye. Out of the 900 participants, 850 patients completed the respective questionnaire, with 375 (44.1%) males and 475 (55.9%) females. Patients were divided into three groups according to their age, specifically below 25 years old (n=353, 41.5%), 25 to 45 years old (247, 29.1%) and above 45 years old (250, 29.4%). Their results showed that the incidence of dry eye disease was significantly higher in females. Additionally, dry eye was more common among elderly people compared to young adults. In their study, the incidence of dry eye disease was different between races; 44% were Malays, 48.1% Chinese, 7.4% Indians and 0.5% from the other races.